OIPE JC79
JUN 17 2003
PATENT & TRADEMARK OFFICE

REQUEST FOR CONTINUED EXAMINATION (RCE) TRANSMITTAL

MAIL STOP RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Subsection (b) of 35 U.S.C. § 132, effective on May 29, 2000, provides for continued examination of an utility or plant application filed on or after June 8, 1995

Application Number	09/744,550
Confirmation Number	9592
Filing Date	January 26, 2001
First Named Inventor	Komei WASHINO
Group Art Unit	1617
Examiner Name	Lauren Q. WELLS
Matter Number	Q62780
Title	DRUGS FOR MEDICAL USE ENABLING NUCLEAR MAGNETIC RESONANCE DIAGNOSIS BY SCALAR COUPLING

#16 MD 6-24-03

This is a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114 of the above-identified application.

1. SUBMISSION REQUIRED UNDER 37 C.F.R. § 1.114

a. ☑ Previously submitted
- i. ☑ Please enter and consider the amendment(s)/reply under 37 C.F.R. § 1.116 previously filed on April 17, 2003
- ii. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
- iii. ☑ Other **The Information Disclosure Statement filed on December 6, 2002 and the Declaration Under 37 C.F.R. § 1.132 filed April 17, 2003**

b. ☑ Enclosed
- i. ☑ Amendment/**Reply Under 37 C.F.R. § 1.114**
- ii. ☐ Affidavit(s)/Declaration(s)
- iii. ☐ Information Disclosure Statements (IDS)
- iv. ☐ Petition for Extension of Time
- v. ☐ Other _____

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2. MISCELLANEOUS

a. ☐ Suspension of action on the above-identified application is requested under 37 C.F.R. § 1.103(c) for a period of _____ months

b. ☐ Other _____

3. FEES

A check for the RCE statutory fee of $750.00 is attached. The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account. A duplicate copy of this transmittal letter is attached.

CORRESPONDENCE ADDRESS

Direct all correspondence to the address for SUGHRUE MION, PLLC filed under the Customer Number listed below:

06/18/2003 MDAMTE1 00000071 09744550
01 FC:1801 750.00 OP

SIGNATURE OF ATTORNEY

Name Sheldon I. Landsman Registration No. 25,430

Signature Sheldon I. Landsman Date June 17, 2003

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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#17
RKO
6-24-03

In re application of

Komei WASHINO, et al.

Appln. No.: 09/744,550

Confirmation No.: 9592

Filed: January 26, 2001

Docket No: Q62780

Group Art Unit: 1617

Examiner: Lauren Q. WELLS

For: DRUGS FOR MEDICAL USE ENABLING NUCLEAR MAGNETIC RESONANCE DIAGNOSIS BY SCALAR COUPLING

REPLY UNDER 37 C.F.R. § 1.114

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In addition to entering and considering the Amendment Under 37 C.F.R. § 1.116 filed on April 17, 2003 and the Declaration filed therewith, applicants request the Examiner to consider the following additional remarks. (Applicants note that in the Amendment Under 37 C.F.R. § 1.116 filed on April 17, 2003, at page 10, fifth line from the bottom, the word "is" should be inserted after "Hopkins et al", and at page 14, line 9, the word "shell" should be "skill").

The Examiner states in the Advisory Action of April 28, 2003 that the Declaration filed April 17, 2003 is not persuasive, because the Declaration provides no comparative data with the prior art.

Applicants point out, however, that the Examiner has completely misunderstood the purpose of the Declaration. The additional experiments described in the Declaration are not directed to compare the present invention with the prior art.

From the very first, none of the prior references provides a conception that the biodistribution of the solvent itself administered to a living body varies depending upon the combination of the solute and the solvent. The present invention enables to detect the biodistribution of the solvent from outside of the living body. Applicants filed the Declaration with the previous Amendment Under 37 C.F.R. § 1.116 on April 17, 2003, in order to prove the effect of the present invention.

The additional experiments mentioned in the Declaration are directed to demonstrate the effect of the present drug composition, that the biodistribution of the solvent itself administered to a living body varies depending upon the combination of the solute and the solvent in the drug composition of the present invention, and the difference in the biodistribution of the solvent can be detected from outside of the living body according to the present drug composition. Therefore, the additional experiments in the Declaration were conducted to demonstrate that the biodistribution of the solvent in the present drug composition was different depending on the combination of the solvent and solute, using two kinds of the present drug compositions comprising different solutes (D-mannitol injection and KM replenisher 4A). It is clearly understood that the biodistribution of the solvent enables a detection by nuclear magnetic resonance, as the biodistribution of the solvent is different.

None of the prior references discloses or suggests the drug composition of the present invention, wherein the biodistribution of the solvent itself administered to a living body varies

depending upon the combination of the solute and the solvent in the drug composition, and the difference in the biodistribution of the solvent can be detected from outside of the living body. Applicants submit that the additional experiments in the Declaration demonstrate the realizability of the present drug composition, and support the novelty and unobviousness of the present invention.

That is, the results given by the additional experiments in the Declaration (i.e., the fact that the biodistribution of the solvent itself administered to a living body varies depending upon the combination of the solute and the solvent in the drug composition) closely relate to the description on page 12, lines 3 to 16 of the present specification as originally filed. The description on page 12, lines 3 to 16 is as follows:

> ...in the case of infusion, which is used as the substituent of blood transfusion from the viewpoint of replenishing water, it is important how it spreads throughout a living body. In the case of an electrolyte infusion, which is of many varieties according to the kind and the concentration of the electrolyte contained therein, a proper drug must be selected for each patient to improve the disease state. In such an instance, by using the present drug in which the whole or a part of water as a solvent has been substituted with ^{17}O, it becomes possible to judge an electrolyte infusion of what composition is to be used for improving the disease state of each patient.

For example, as for an electrolyte infusion, the biodistribution of the infusion administered to a living body varies depending on the kind and the concentration of the electrolyte contained therein. Accordingly, by using the infusion comprising ^{17}O-containing water as a solvent (i.e., ^{16}O in the water as a solvent has been substituted with ^{17}O), the present drug composition enables to detect the biodistribution of the electrolyte infusion containing various kinds and concentrations of the electrolytes, then to contribute to a proper selection of the kind and concentration of the electrolytes in the drug composition, being suitable to improve

the disease state of each patient. As for a drug composition, comprising drug as a solute and water as a solvent, the biodistribution of the water as a solvent is different depending on the kind and concentration of the solute and/or a combination of the solvent and solute, and besides the effect of the drug composition in a living body varies depending upon the circumstance.

The biodistribution of the water as a solvent and the effect of the drug administered to a living body vary depending upon a combination of the solute and solvent in a drug composition. In other words, the biodistribution of the water as a solvent and the effect of the drug administered to a living body vary depending upon the constituents of the drug composition. The drug composition of the present invention is the one enabling to detect said difference in the biodistribution by nuclear magnetic resonance.

According to the present drug composition, the information on circulation and biodistribution of the drug in vivo can be confirmed simultaneously with the administration of the therapeutic drug to each patient. Further, the information on circulation and distribution of the drug in vivo can be confirmed by administering the present drug composition before the administration of the objective therapeutic drug to each patient, as well. Accordingly, the present drug composition contributes to an estimation of the effect of the medicaments and a proper selection of the medicaments.

Applicants submitted the additional experiments in the Declaration filed April 17, 2003, in order to prove the above-mentioned argumentation. The two solutes of "D-mannitol injection (osmotic diuretic)" and "KN replenisher 4A (postoperative restoring liquid)" used in the additional experiments of the Declaration are representative infusions to regulate the biodistribution of water in a living body. In the additional examples of the Declaration, two

kinds of the drug compositions wherein the solutes were different from each other were formulated, and the biodistribution of the ^{17}O-containing water as a solvent was determined in various organs in rat.

In view of the above, applicants submit that the present application is allowable.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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Date: June 17, 2003